General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for ivacaftor therapy in the context of *CFTR* genotype.

Bibliographic Source(s)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Approximately 1,900 disease-causing cystic fibrosis transmembrane conductance regulator protein (*CFTR*) variants have been identified (see Supplementary Table S1 online [see the "Availability of Companion Documents" field]) and have been extensively studied in multiple geographically, racially, and ethnically diverse cystic fibrosis (CF) patients. Despite the large number of *CFTR* variants, most can be grouped into classes that have shared features (see Table 1 below).

Table 1. *CFTR* Variant Classes and Strategies to Restore Function

CFTR Variant	Nature of Defect	Example	Treatment Strategy
Class I	Biosynthesis[a]	G542X	Suppress premature termination codon
Class II	Folding and trafficking	F508del	Restore folding
Class III	Gating	G551D	Restore gating
Class IV	Conductance	R117H	Increase pore size
Class V	Reduced splicing efficiency	5T[b], 2789 + 5 G>A	Increase splicing efficiency
Class VI	Shortened time at plasma membrane	F508del[c] (corrected)	Stabilize protein at plasma membrane

[a]Other biosynthesis defects include frameshift mutations that would not be predicted to be influenced by stop codon suppression. [b]5T refers to the thymidine tract at the end of

intron 8 (intron 9 when counting exons sequentially without subletters), which subsequently influences the splicing of exon 9 (exon 10) of CFTR. Described tract lengths include 5T, 7T, and 9T, with more efficient splicing exhibited with longer thymidine tracts. The thymidine tract status can be an important contributor to variant phenotype. For example, R117H *CFTR* with a 9T thymidine tract typically does not cause CF. By contrast, R117H *CFTR* with a 5T thymidine tract typically does cause CF, and R117H *CFTR* with a 7T thymidine tract is variably associated with CF. See Supplementary Table S1 online (see the "Availability of Companion Documents" field) for mapping details. [c]Evidence suggests that *F508del-CFTR* demonstrates reduced stability at the plasma membrane and rapid internalization following correction of folding and trafficking.

Adapted from Clancy, J.P. & Jain, M. Personalized medicine in cystic fibrosis: dawning of a new era. Am. J. Respir. Crit. Care Med. 186, 593–597 (2012).

Genetic Test Interpretation

Patients with CF may have undergone prenatal screening or a genetic test to determine the underlying variants of their condition, and results of these genetic tests can be used to guide therapy for ivacaftor treatment. The current guidelines focus on the interpretation of genetic tests for the presence of *G551D-CFTR, G1244E-CFTR, G1349D-CFTR, G178R-CFTR, G551S-CFTR, S1251N-CFTR, S1255P-CFTR, S549N-CFTR, S549R-CFTR*, and *F508del-CFTR* variants. For more information regarding screening for CF, see the Supplementary Material online (see the "Availability of Companion Documents" field).

The wealth of information regarding how various mutations disrupt CFTR function is beginning to help clinicians to categorize CF patients for viable therapeutic strategies. *F508del-CFTR* (Δ-F508, p.F508del, c.1521_1523delCTT (rs113993960), and c.1520_1522delTCT (rs199826652)) is the most common *CFTR* variant (see Supplementary Tables S1, S2, and S3 online [see the "Availability of Companion Documents" field]. It is primarily a class II variant that is caused by the deletion of a phenylalanine at position 508 in the CFTR protein (Cystic Fibrosis Foundation, 2011 Patient Registry Report). The *F508del-CFTR* variant disrupts CFTR protein folding and processing, blocking maturation of the protein and localization to the plasma membrane. *G551D-CFTR* (p.G551D, c.1652G>A, rs75527207 allele A) is the third most common *CFTR* variant and is present in 4.4% of CF patients. It is a single-nucleotide change that causes a glycine to aspartic acid amino acid change at position 551 of the CFTR protein, resulting in a class III (gating) variant capable of localizing to the epithelial cell surface but with defects in ATP binding and hydrolysis (by the nucleotide-binding domains) such that G551D-CFTR fails to transport chloride normally (Cystic Fibrosis Foundation, 2011 Patient Registry Report).

Therapeutic Recommendations

After the submission and review of the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline manuscript, the U.S. Food and Drug Administration (FDA)-approved drug label for ivacaftor was updated to include additional variants. In light of these changes, the CPIC guideline annotation on PharmGKB (https://www.pharmgkb.org/guideline/PA166114461) has been updated to include additional *CFTR* variants, specifically G1244E (rs267606723), G1349D (rs193922525), G178R (rs80282562), G551S (rs121909013), S1251N (rs74503330), S1255P (rs121909041), S549N (rs121908755) and S549R (rs121908757 and rs121909005). These variants are not discussed in the 2014 guideline publication but are discussed in this summary.

The evidence outlined in Supplementary Table S4 online (see "Availability of Companion Documents" field) provides the basis of the therapeutic recommendations detailed in Table 2 (see below) and Figure 1 in the original guideline document (an updated version of Figure 1 including variants listed above is provided at https://www.pharmgkb.org/guideline/PA166114461). Ivacaftor treatment is recommended only in CF patients who are either homozygous or heterozygous for the *G551D-CFTR, G1244E-CFTR, G1349D-CFTR, G178R-CFTR, G551S-CFTR, S1251N-CFTR, S1255P-CFTR, S549N-CFTR, and S549R-CFTR* variants. This recommendation is based on the results of a small number of clinical trials that selected for patients with the *G551D-CFTR* variant and on recommendations by regulatory bodies. Furthermore, one study demonstrated a lack of clinical effect in patients with two copies of the *F508del-CFTR* variant; however, this study was underpowered to evaluate efficacy. This recommendation is also supported by the mechanism of action of ivacaftor, identified through drug screening as potentiating the gating function of mutant *CFTR*, and subsequent *in vitro* studies showing that ivacaftor enhances G551D-CFTR activity.

These recommendations are consistent with the FDA and European Medicines Agency labeling for ivacaftor (see http://www.pharmgkb.org/drug/PA165950341?tabType=tabDrugLabels), in which the drug is indicated for use in CF patients who have a *G551D-CFTR* variant on at least one allele and is not recommended for those without a *G551D-CFTR* variant, including those homozygous for the *F508del-CFTR* variant. Both labels state that if genotype is unknown, accurate genetic testing of CFTR should be carried out before treatment with ivacaftor. In addition, the European Medicines Agency drug label states that the drug should be prescribed only by physicians who have experience in CF treatment.

Clinical trials of ivacaftor in patients with the *G551D-CFTR* variant were carried out in CF patients who were (i) 12 years and older and (ii) aged 6–11 years. The safety of the drug has not been established in children younger than 6 years of age; therefore, the recommendations in Table 2 (see below) are inclusive of pediatric patients aged 6 years and older, as well as in adults.

Recommendations for Incidental Findings

The *G551D-CFTR* variant is associated with CF and pancreatic insufficiency (when a nonfunctional CFTR variant is found on the other allele)

(http://www.CFTR2.org⬚). Patients should discuss their genotype results with a CF physician and/or a genetic counselor. Furthermore, genetic counseling is important for families with children diagnosed with CF and also for families of children who are carriers for CF variants, so that they can understand their risks of CF in future pregnancies.

Table 2. Prescribing Ivacaftor Based on CFTR Genotype for Patients with Cystic Fibrosis

Adapted from Table 2 of the 2014 guideline manuscript (April 2014 Update on PharmGKB: https://www.pharmgkb.org/guideline/PA166114461 ⬚). Variants have been added to the table below that are not in the published 2014 guideline or supplement; specifically, variants other than G551D and F508del.

CFTR Genotype	Implications for Ivacaftor Effects	Therapeutic Recommendations	Classification of the Recommendations
Homozygous or heterozygous *G551D-CFTR*—e.g., G551D/F508del, G551D/G551D, rs75527207 genotype AA or AG	Significant improvement in lung function, weight, risk of pulmonary exacerbation, and patient reported outcomes, and reduction in sweat chloride concentrations through enhanced CFTR channel activity (increased probability of open channel)	Use ivacaftor according to the product label (e.g., 150 mg every 12 h for patients aged 6 years and older without other diseases; modify dose in patients with hepatic impairment)	Strong
Homozygous for *F508del-CFTR (F508del/F508del)*, rs113993960, or rs199826652 genotype del/del	No significant reduction in sweat chloride concentrations; no changes in other clinical measurements, including spirometric measurements, pulmonary exacerbations, or body weight.[b] Unlikely to respond to treatment	Ivacaftor is not recommended[a]	Moderate[b]
Homozygous or heterozygous for one of the following *CFTR* variants that affect gating: *G1244E-CFTR* (rs267606723 genotype AA or AG), *G1349D-CFTR* (rs193922525 genotype AA or AG), *G178R-CFTR* (rs80282562 genotype AA or AG), *G551S-CFTR* (rs121909013 genotype AA or AG), *S1251N-CFTR* (rs74503330 genotype AA or AG), *S1255P-CFTR* (rs121909041 genotype CC or CT), *S549N-CFTR* (rs121908755 genotype AA or AG), *S549R-CFTR* (rs121909005 genotype GG or GT, rs121908757 genotype CC or CA)[c]	Significantly enhanced channel open probability in vitro. In vitro assays with CFBEo- cells expressing S549N-CFTR showed ivacaftor potentiated chloride channel function, and a case study showed improved lung function after ivacaftor treatment in a 12-year-old girl with CF with a copy of the S549N variant.	Use ivacaftor according to the product label (e.g., 150 mg every 12 hours for patients age 6 and older without other diseases; modify dose in patients with hepatic impairment).	Moderate

[a]These recommendations are based on treatment of CF patients with ivacaftor alone and on current evidence. Clinical trials are currently under way to investigate ivacaftor alone or in combination with other drugs to treat CF patients with CFTR variants other than G551D; therefore, there is potential that ivacaftor may be effective in these patients. See main text for further details. [b]The recommendation for patients with the F508del/F508del genotype is based on ivacaftor mechanism of action and clinical observational data. The clinical study, however, was a safety study and was not powered to detect a difference in efficacy. [c]Variants listed in this table include those added to the amended drug label for ivacaftor which was approved by the FDA on February 21, 2014. The modifications to this table were made after the acceptance of publication of the 2014 CPIC Ivacaftor-CFTR guideline and are not reflected in the PDFs of the CPIC guideline main manuscript or supplement.

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

An algorithm titled "Treatment Algorithm for Clinical Use of Ivacaftor for Cystic Fibrosis Patients Based on *CFTR* Genotype" is provided on the Pharmacogenomics Knowledgebase Web site [   ].

Scope

Disease/Condition(s)

Cystic fibrosis (CF)

Guideline Category

Counseling

Evaluation

Screening

Treatment

Clinical Specialty

Endocrinology

Gastroenterology

Internal Medicine

Medical Genetics

Pediatrics

Pharmacology

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide information to facilitate the interpretation of genotype tests in order to guide ivacaftor therapy

Note: Detailed guidelines for the use of ivacaftor as well as analyses of cost-effectiveness are beyond the scope of this document.

Target Population

Cystic fibrosis (CF) patients with particular cystic fibrosis transmembrane conductance regulator protein (CFTR) variants, G551D-CFTR(rs75527207), G1244E-CFTR (rs267606723), G1349D-CFTR (rs193922525), G178R-CFTR (rs80282562), G551S-CFTR (rs121909013), S1251N-CFTR (rs74503330), S1255P-CFTR (rs121909041),S549N-CFTR (rs121908755), and S549R-CFTR (rs121908757 and rs121909005)

Interventions and Practices Considered

Ivacaftor therapy in the context of cystic fibrosis transmembrane conductance regulator protein (CFTR)

Major Outcomes Considered

- Improvement in lung function, weight
- Pulmonary exacerbation
- Reduction in sweat chloride concentrations

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The authors searched the PubMed database (1966 to June 2013 and Ovid MEDLINE (1950 to June 2013) for keywords (((((((((((((((((((cftr) OR atp binding cassette sub family g member 7) OR atp binding cassette sub family g, member 7) OR atp binding cassette transporter subfamily a member 7) OR atp-binding cassette, subfamily c member 7) OR camp-dependent chloride channel) OR channel conductance-controlling atpase) OR cystic fibrosis transmembrane conductance regulator) OR cystic fibrosis transmembrane conductance regulator) OR atp-binding cassette AND (sub-family c, member 7)) OR ABC35) OR ABCC7) OR CF) OR cftr/mrp) OR MRP7) OR tnr-cftr) OR dJ760C5.1) OR OTTHUMP00000196524)) AND (((ivacaftor) OR vx-770) OR kalydeco) and ((ivacaftor) OR vx-770) OR Kalydeco. Results were limited to those available in English.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

The evidence summarized in Supplemental Table S4 (see the "Availability of Companion Documents" field) has been graded on a scale of high, moderate, and weak, modified slightly from Valdes et al (see the "Rating Scheme for the Strength of the Evidence" field)

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Clinical Pharmacogenetics Implementation Consortium (CPIC) dosing recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines.

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. The authors chose to use a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents found at http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Potential Benefits for the Patient

Benefits include identifying patients who are eligible for and could benefit from ivacaftor treatment. This genotype information may also contribute to understanding a patient's pathophysiology and therapeutic options.

Potential Harms

Potential Risks for Patients

Patients with the aforementioned cystic fibrosis transmembrane conductance regulator protein (*CFTR*) variants are still at risk of not responding to ivacaftor treatment, and treatment outcomes vary between patients. Unfortunately, CFTR biomarkers (sweat chloride levels and nasal potential difference) did not correlate with clinical response in the phase II and phase III trials of ivacaftor in *G551D-CFTR* patients (forced expiratory volume in 1 s, weight, risk of pulmonary exacerbations, or patient-reported outcomes). For patients without these *CFTR* variants, ivacaftor is not indicated. However, several drugs targeting other *CFTR* variants are currently under development or in clinical trials and may benefit these patients in the future.

Caveats: Appropriate Use AND/OR Potential Misuse of Genetic Tests

- Errors may occur in *CFTR* genotyping or in the reporting of results. If so, a patient may be subjected to ineffective ivacaftor treatment or may be omitted from potentially effective treatment with ivacaftor. The U.S. Food and Drug Administration (FDA) label states that an FDA–cleared test should be carried out if a patient's genotype is unknown. Genetic test results should include coverage for *G551D-CFTR* (rs75527207), *G1244E-CFTR* (rs267606723), *G1349D-CFTR* (rs193922525), *G178R-CFTR* (rs80282562), *G551S-CFTR* (rs121909013), *S1251N-CFTR* (rs74503330), *S1255P-CFTR* (rs121909041), *S549N-CFTR* (rs121908755) and *S549R-CFTR* (rs121908757 and rs121909005) in order to follow the Clinical Pharmacogenetics Implementation Consortium (CPIC) ivacaftor guidelines.
- Other genetic and environmental factors may affect a patient's response to ivacaftor. Although traditionally considered a monogenic disease, cystic fibrosis (CF) has a complex phenotype. CFTR itself has many roles, defects in other genes may be involved, and many physiological pathways affect a CF patient's life span and response to therapy. Patients are still likely to require concomitant medications to treat the other accompanying disease manifestations and associated infections of CF. Drug–drug interactions may occur that affect ivacaftor efficacy and/or toxicity when taken in combination with other medications, in particular CYP3A inhibitors or inducers (http://www.pharmgkb.org/drug/PA165950341?tabType=tabDrugLabels), and conversely, ivacaftor may affect the efficacy and/or toxicity of concomitant therapies.

Qualifying Statements

Qualifying Statements

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. The CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC guidelines, or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Resources

> For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

> Clancy JP, Johnson SG, Yee SW, McDonagh EM, Caudle KE, Klein TE, Cannavo M, Giacomini KM. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for ivacaftor therapy in the context of CFTR genotype. Clin Pharmacol Ther. 2014 Jun;95(6):592-7. [40 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)

Source(s) of Funding

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Guideline Committee

Not stated

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Financial Disclosures/Conflicts of Interest

J.P.C's institution (Cincinnati Children's Hospital Medical Center) receives contract research support from Vertex Pharmaceuticals for the conduct of cystic fibrosis (CF) clinical trials. He has served as a scientific advisor to Vertex Pharmaceuticals and has provided educational presentations regarding the appropriate use of Kalydeco. The other authors declared no conflict of interest.

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Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Pharmacogenomics Knowledgebase Web site   .

Availability of Companion Documents

Supplementary material, including tables and methodological information, is available from the Pharmacogenomics Knowledgebase Web site   .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 7, 2014. The information was verified by the guideline developer on November

6, 2014.

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